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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50 and 56

[Docket No. FDA-2000-N-0009] (formerly 2000N-0074)

RIN 0910-AG71

Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to provide additional safeguards for children enrolled in clinical investigations of FDA-regulated products. This rule finalizes the interim rule published in 2001 to bring FDA regulations into compliance with provisions of the Children's Health Act of 2000 (the Children's Health Act). The Children's Health Act requires that all research involving children that is conducted, supported, or regulated by the Department of Health and Human Services (HHS) be in compliance with HHS regulations providing additional protections for children involved as subjects in research. FDA is taking this action both to comply with the congressional mandate and because of increases in the enrollment of children in clinical investigations as a result of ongoing pediatric initiatives.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

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I. Background

In the Federal Register of April 24, 2001 (66 FR 20589), FDA published an interim rule amending its regulations to provide additional safeguards for children enrolled in clinical investigations of FDA-regulated products (part 50 (21 CFR part 50, subpart D (FDA subpart D))). The interim rule brought FDA regulations into compliance with provisions of the Children's Health Act (Public Law 106-310). Title XXVII, section 2701 of the Children's Health Act required that within 6 months of its enactment all research involving children conducted, supported, or regulated by HHS be in compliance with HHS regulations providing additional protections for children involved as subjects in research (45 CFR part 46, subpart D (HHS subpart D)). The interim rule was effective on April 30, 2001. Interested parties were given until July 23, 2001, to comment on the interim rule.

FDA is finalizing its interim final rule both to comply with the congressional mandate in the Children's Health Act and because of increases in the enrollment of children in clinical investigations, in part as a result of ongoing pediatric initiatives. Some of these pediatric initiatives were described in detail in the interim rule (66 FR 20589), including the Food and Drug Administration Modernization Act of 1997 (FDAMA) and FDA's 1998 pediatric rule (63 FR 66632, December 2, 1998).

FDAMA established economic incentives for manufacturers to conduct pediatric studies on drugs for which exclusivity or patent protection is available under the Drug Price Competition and Patent Term Restoration Act (Public Law 98-417) or the Orphan Drug Act (Public Law 97-414). These provisions add 6 months of marketing exclusivity (known as pediatric exclusivity) to any existing exclusivity or patent protection on a drug moiety for which FDA has requested pediatric studies and the manufacturer has conducted such studies in accordance with the requirements of the statute. This exclusivity-based incentive was re-authorized under the Best Pharmaceuticals for Children Act (BPCA) of 2002 (Public Law No. 107-109) and 2007 (Title V of Public Law 110-85). The Patient Protection and Affordable Care Act of 2010 (section 7002(g)(1) of Public Law 111-148) extended pediatric exclusivity and applicable provisions of BPCA 2007 to biological products. Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144) made permanent this exclusivity-based incentive for studies conducted in response to a written request from FDA.

Under FDA's 1998 pediatric rule, drug and biological product approvals issued, or applications submitted, on or after April 1, 1999, for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, were required to include pediatric assessments for all indications for which applicants were receiving or seeking approval, unless the requirement was waived or deferred. Although the pediatric rule was suspended by court order on October 17, 2002, the Pediatric Research Equity Act (PREA) of 2003 (Public Law 108-155) codified many of its elements. The Pediatric Research Equity Act of 2007 (Title IV of Public Law 110-85) re-authorized and expanded PREA 2003, continuing these pediatric requirements. FDASIA also made permanent this requirement for pediatric assessments.

Additionally, as noted in the interim final rule, FDA initiated other actions to encourage the development of adequate pediatric use information for FDA-regulated products, for example, through issuance in 2000 of pediatric guidance titled “E11 Clinical Investigation of Medicinal Products in the Pediatric Population” (ICH E11) (December 2000) (Ref. 1). This guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as part of the ICH effort to harmonize such requirements among the European Union, Japan, and the United States. ICH E11 addresses issues in pediatric drug development including ethical considerations in pediatric studies. It states that pediatric populations represent a vulnerable subgroup and special measures therefore are needed to protect the rights of pediatric study participants. Section 2.6 of ICH E11 addresses relevant issues including: the roles and responsibilities of institutional review boards (IRBs) and independent ethics committees (IECs), recruitment of study participants, consent and assent, and minimizing risk and distress in pediatric studies.

Additional examples of pediatric specific guidance include: (1) A final guidance entitled “Acute Bacterial Otitis Media: Developing Drugs for Treatment” (September 2012) (Ref. 2), which includes a section on the ethical considerations under part 50, subpart D in designing a clinical trial for acute bacterial otitis media; and (2) a final guidance entitled “Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children” (March 2007) (Ref. 3), which includes a section on the ethical concerns raised by the choice of a comparator or control group for allergic rhinitis and asthma studies.

These (and other) regulatory actions, combined with the statutory initiatives described previously, have resulted in increases in the enrollment of children in clinical investigations (see information provided at <http://www.fda.gov/pediatrics>).

II. Highlights of the Final Rule

This final rule adopts the safeguards described in HHS subpart D for children participating in clinical investigations regulated by FDA under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C 355(i) and 360j(g)) , as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA, including human drug and biological products; medical devices for human use; foods, including dietary supplements, that bear a nutrient content claim or health claim; infant formula; food and color additives; and electronic products. (See § 50.1) These safeguards are intended to ensure that the rights and welfare of children who participate in clinical investigations are adequately protected. Nothing in these regulations is intended to preempt any applicable Federal, State, or local laws that require additional safeguards for children participating in clinical investigations.

The final rule brings FDA's regulations into compliance with HHS subpart D, as directed by Congress, with some changes reflecting differences between FDA's and HHS's regulatory authority and other changes made for clarification. In the preamble to the interim rule, we provided a detailed explanation of the provisions of the rule. In the final rule, we respond to comments received on the interim rule. Four substantive changes have been made to the codified section of the final rule: (1) The definition of guardian has been modified, (2) the definition of permission has been modified, (3) paragraph (a) has been added to § 50.51 to require, consistent with § 46.404 of HHS subpart D, that IRBs assess the level of risk to children in clinical investigations subject to § 50.51, and (4) a phrase has been added to § 50.55(e) to make it clear that the exception for emergency research described in § 50.24 applies to research in children. In addition, we have made changes on our own initiative for the purposes of clarity and

consistency. In addition to modifying the definitions of guardian and permission, changes to the following sections were made in order to be more consistent with HHS 45 CFR part 46, subpart D: 1) Changing “may” to “should” in the definition of assent (§ 50.3(n)); (2) deleting “and documents” from §§ 50.51 to 50.54; and (3) deleting “if consistent with State law” from § 50.55(e)(1).

III. Comments and Agency Response

The Agency received a total of 18 comments on the April 24, 2001, interim rule. Five of those comments were from pharmaceutical companies, four were from health care professionals, four were from national membership organizations, three were from Federal Government agencies, one was from a State legislator, and one was from a private citizen. The majority of comments supported the rule. Most commenters provided comment on specific provisions, including the areas on which FDA solicited comment.

A. Definitions

(Comment 1) We received one comment stating that our modification of definitions creates several regulatory documents that are using slightly different terms and definitions. The comment stated that these differences would create challenges for sponsors as they try to meet the requirements under one document but, due to slightly modified terms and definitions, fail to meet requirements under another document.

As we stated in the preamble to the interim rule, we are aware that dissimilar or inconsistent Federal requirements governing pediatric protections could be burdensome to institutions, IRBs, and the process of clinical investigation (66 FR 20589 at 20591). The majority of modifications in the interim rule to definitions from HHS subpart D were made only to the extent necessary to make it clear that the definitions apply to participation in clinical

investigations regulated by FDA under sections 505(i) and 520(g) of the FD&C Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA. This final rule modifies some of the definitions in the interim rule, resulting in greater consistency between HHS and FDA definitions, as discussed further in this document.

1. Permission

(Comment 2) Two comments supported our definition of “permission” at § 50.3(r) and agreed that it was necessary to adopt this term. We agree with those comments. However, we have decided to simplify the definition by deleting the statement that permission must be obtained in compliance with part 50, subpart B and must include the elements of informed consent described in § 50.25. As required under § 50.55(f), permission by parents or guardians must be documented in accordance with, and to the extent required by, § 50.27, and thus must include the elements of informed consent required by § 50.25. The identified language is therefore unnecessary. As a result of this change, this definition and the definition of parental permission found in 45 CFR 46.402(c) are the same.

2. Guardian

We defined “guardian” at § 50.3(s). In the preamble to the interim rule, we explained that we were adopting the term because it is currently used in HHS subpart D and is familiar to IRBs. Our regulations at § 50.3(l) use the term “legally authorized representative” to describe an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research. Our definition of the term guardian was intended to make it clear that, for purposes of FDA subpart D, a guardian must be an individual who is legally authorized to consent to a child’s

participation in research. We invited comment on our definition and any implications under State or local law.

(Comment 3) We received five comments on our definition of guardian. All five comments raised concerns about our inclusion of language stating that a guardian is an individual who is authorized to consent on behalf of a child to participate in research.

Two comments recommended that the definition of guardian at § 50.3(s) should be the same as, or consistent with, the definition of guardian at 45 CFR 46.402(e) of HHS subpart D. One comment noted that under HHS subpart D, IRBs have been and continue to be responsible for ensuring that HHS-sponsored or HHS-conducted studies involving children comply with Federal, State, and local legal standards regarding permission. The comment stated that it was unclear why a revised definition was necessary in our regulation when no change is proposed for the existing definition in the HHS regulation. The comment stated that when HHS-sponsored research is also subject to FDA regulation, the conflicting definitions will lead to confusion. The second comment stated that our definition of guardian may result in unanticipated consequences, since many State laws do not specifically authorize legal guardians to provide consent to research. The comment stated that this requirement would unnecessarily prevent some children with guardians from participating in research from which they could benefit directly.

Another comment stated that the additional language we suggested represented a departure from the HHS definition and that it was unclear whether State laws specifically authorize guardians to consent to children's participation in clinical research. The comment stated that FDA's change may represent a serious, unintended obstacle to children's participation in research. The comment suggested defining a guardian as an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care and

whose consenting on behalf of the child to research participation is consistent with applicable laws, if any.

Two comments stated that our definition leaves open the possibility that a guardian could be a person who is authorized to consent to a child's participation in research, but not authorized to consent to general medical care. These comments stated that this would be wholly undesirable for the child and that the language should be clarified to require that no one may consent to a child's participation in research who is not also authorized to consent to the child's general medical care. These comments also stated that it appears that many State laws do not specifically authorize a guardian to permit a child's involvement in research, so the definition may be very restrictive in practice. These comments concluded that adequate protection for children would result from the requirement that guardians should be authorized to consent to general medical care and that they should be in loco parentis, with a legally enforceable duty to care for the totality of the child's interests.

We appreciate the comments we received on State and local laws of guardianship and the likelihood that many of these laws do not specifically grant guardians the authority to consent to research. We did not intend to create an obstacle to children's participation in research or to prevent children under guardianship from participating in beneficial research when we included authorization to consent to research in the definition of guardian. We also did not intend to suggest that it would be appropriate to allow a person who is authorized to consent to research only, but not authorized to consent to general medical care, to grant permission for a child to participate in FDA-regulated research. We note, however, that we are not aware of any State or local laws which authorize a guardian to consent to research where the guardian does not have the authority to consent to general medical care as well.

After reviewing the comments submitted, we have decided to delete the phrase “when general medical care includes participation in research,” as State and local laws may be silent on whether general medical care includes research participation. We have also deleted the language stating that “a guardian also means an individual who is authorized to consent on behalf of a child to participate in research.” This revised definition makes it clear that under FDA regulations a legally authorized guardian for general medical care may consent on behalf of a child to participate in research in the absence of specific laws granting (or restricting) that authority. It remains the responsibility of an IRB to determine if there are any applicable State or local laws that either grant or restrict that authority. This revised definition of guardian is the same as the definition of guardian in HHS 45 CFR 46.402(e) of HHS subpart D.

B. IRB Membership and Continuing Education

(Comment 4) Two comments stated that IRB membership should include professionals and lay persons with demonstrated competence working with children, including pediatricians, pediatric nurses, pediatric nutritionists, pediatric pharmacologists, pediatric psychologists, nonclinical experts in pediatric issues, and lay persons with a community sensitivity to the pediatric population (e.g., preschool teachers). One comment suggested that an advisory committee with specific expertise in pediatric areas of clinical research be established for IRBs. This comment also stated that processes need to be implemented to orient and educate IRB members on an ongoing basis, as well as standards and procedures for self-evaluation, including performance standards, self-assessment tools, certification, and the development of peer-based accreditation systems. One comment also suggested that all IRB members should complete a course, such as the one offered by the Office for Human Research Protections (OHRP), on IRB members’ roles and responsibilities. This comment suggested that FDA develop a course on

additional safeguards for children for those conducting research within the pediatric population and that an intraregulatory approach between HHS and FDA would provide consistency and uniformity in this educational process.

FDA supports the intent of these comments to ensure IRB members are adequately trained to make decisions on the unique aspects of conducting clinical trials in children. Part 56 (21 CFR part 56) of our regulations addresses IRBs generally. Section 56.107 requires IRBs to have members with varying backgrounds to promote complete and adequate review of research activities. This section requires the IRB to be sufficiently qualified through the experience and expertise of its members, the diversity of its members, and their sensitivity to issues such as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. Section 56.107(a) specifically states that if an IRB regularly reviews research that involves “a vulnerable category of subjects, such as children . . . , consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.” Section 56.107(b) states that no IRB may consist entirely of members of one profession. Section 56.107(c) requires that each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas. FDA Guidance (ICH E11) on “Clinical Investigation of Medicinal Products in the Pediatric Population” advises that “when protocols involving the pediatric population are reviewed, there should be IRB/IEC members or experts consulted by the IRB/IEC who are knowledgeable in pediatric ethical, clinical, and psychosocial issues” (§ 2.6.1, Ref. 1). In our view, these provisions and guidance are adequate to ensure the appropriate composition of members on IRBs reviewing clinical trials in children.

We agree that it is important for members of an IRB reviewing such trials to be educated and trained in appropriate areas. Although these regulations do not require any specific training or continuing education for IRB members, we discuss the programming and educational needs for the IRB and investigator community with OHRP and others on an ongoing basis. As part of our efforts, we will consider the need to develop specific educational programs focusing on research involving children.

With regard to the comment requesting establishment of an advisory committee for IRBs, we note that § 56.107(f) provides that an IRB, at its discretion, may invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available on the IRB. These individuals serve in an advisory capacity and do not vote with the IRB. We have published extensive guidance for IRBs and clinical investigators to use in conducting their reviews. This guidance is available on FDA's Web site at

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/default.htm>.

C. Risk Categories

As stated in the preamble to the interim rule, we adopted HHS subpart D, as directed by Congress, with those changes necessary because of differences between FDA's and HHS's regulatory authority. Sections § 50.51 through § 50.53 describe the criteria under which IRBs may approve clinical investigations of FDA-regulated products in children. Section 50.54 describes the criteria under which a clinical investigation that is otherwise not approvable by an IRB under sections § 50.51 through § 50.53 may be referred to FDA for review and consultation with a panel of experts.

1. Section 50.51--Clinical Investigations Not Involving Greater Than Minimal Risk

We received three comments on § 50.51.

(Comment 5) One comment requested a clearer definition of “greater than minimal risk.” Although it noted that FDA provided examples of types of procedures that fit the category of no more than minimal risk, the comment stated that the term is vague and the definition is open to interpretation.

Another comment stated that the language of this provision deviated in an important way from 45 CFR 46.404 of HHS subpart D, which places responsibility for determining the level of risk with the IRB. The comment stated that FDA only requires the IRB to find and document adequate provisions for soliciting assent and permission, which may create circumstances in which the investigator and the IRB disagree on the level of risk. The comment acknowledged that any disagreement will be resolved by the decision of the IRB, but the provision might cause unnecessary conflict and confusion. The comment also stated that this section appears internally inconsistent with §§ 50.52 and 50.53 in which the IRB assesses the nature and level of risk and suggested that the language of this provision should be consistent with 45 CFR 46.404 of HHS subpart D.

Another comment stated that the rule should include a well-defined scale system for risk assessment that would allow the IRB to classify procedures and help in identifying the degree of minimal risk. As an example, the comment stated that collecting a clean-catch urine sample via a catheter has a potential to cause tissue injury and/or infection and therefore has a higher degree of risk than testing devices involving temperature readings orally or in the ear. The comment stated that this type of scale would help IRBs in granting an approval for a procedure by providing a specific “distinction” of the potential risk.

As stated in the preamble to the interim rule (66 FR 20589 at 20593), we previously adopted HHS's definition of minimal risk without change in § 50.3(k). The definition of minimal risk states that "minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." As one comment noted, in the preamble to the interim rule we provided examples of procedures and clinical investigations that may present no greater than minimal risk to children.

While we acknowledge that there is no specific definition of "greater than minimal risk" in these regulations, IRBs are familiar with this category of research and have been applying it for many years. Given this reality, we decline to add a definition of "greater than minimal risk" to our regulations at this time.

The Children's Health Act also required a substantive review of HHS subpart D, and required the Secretary to consider any necessary modifications to ensure adequate and appropriate protection of children participating in research. This review was conducted by OHRP and a report was submitted to Congress in May 2001 entitled "Protections for Children in Research: A Report to Congress in Accord with Section 1003 of P.L. 106-310, Children's Health Act of 2000" (2001 OHRP report) (Ref. 4). While the 2001 OHRP report concluded that the current HHS regulations under subpart D are sound, effective, and well-crafted, the report identified terms and concepts for which further guidance is needed. Among the terms and concepts identified in this report as needing clarification are the terms "minimal risk" and "minor increase over minimal risk."

On January 4, 2002, the President signed BPCA 2002 into law. BPCA 2002 required HHS to contract with the Institute of Medicine (IOM) to conduct a review of Federal regulations relating to research involving children and report its findings to Congress. In the conduct of this review, the IOM was required to consider the definition of minimal risk with respect to children. The IOM published its report, “Ethical Conduct of Clinical Research Involving Children” in 2004 (2004 IOM report) (Ref. 5). The 2004 IOM report recommended that the Secretary's Advisory Committee on Human Research Protections continue the work of its predecessor committee (the National Human Research Protections Advisory Committee) by developing additional consensus descriptions of procedures or interventions that present minimal risk and no more than a minor increase over minimal risk. The 2004 IOM report also recommended that OHRP and FDA cooperate to develop and disseminate guidance and examples for investigators and IRBs to clarify definitions, including the definitions of minimal risk and minor increase over minimal risk (2004 IOM report, p. 136) (Ref. 5).

While both the 2001 OHRP report and the 2004 IOM report recommended that further guidance may be appropriate to clarify the meaning of minimal risk, neither report recommended changes to the current regulatory definition of minimal risk. Although we will not change FDA's definition of minimal risk at this time, we will consider developing guidance to assist in determining whether a research intervention poses minimal or more than minimal risk to children.

We agree with the comment regarding the fact that § 50.51 does not specifically require IRBs to assess the level of risk in order to approve a study under that provision. We have modified § 50.51 to make clear that it applies to clinical investigations involving children as subjects where the IRB finds that no greater than minimal risk to children is presented. This

change is consistent with § 46.404 of HHS subpart D and §§ 50.52 and 50.53 of our regulations, and clarifies that the IRB is responsible for reviewing, assessing, and documenting the nature and level of risk in this category. Furthermore, because an IRB is required to document its findings under § 56.115(a)(2), we also have deleted the phrase “and documents” as unnecessary, and have made the same change to §§ 50.51 through 50.54.

While we appreciate the intent of the comment requesting a scale system for assessing risk, attempting to identify and classify every procedure that might be used in a clinical investigation as to its appropriate risk category would be a difficult, if not impossible, task. Rather, the broad categories laid out in the regulation will assist IRBs in assessing the risk level for any specific intervention and/or procedure in a clinical investigation on a case-by-case basis. IRBs have been using this system of classification for many years. However, if HHS proposes to change these risk categories, we will review and consider modifying the corresponding provisions of our regulations as appropriate.

2. Section 50.52--Clinical Investigations Involving Greater Than Minimal Risk, But Presenting the Prospect of Direct Benefit to Individual Subjects

In our discussion of § 50.52 in the preamble to the interim rule (66 FR 20589 at 20593), we recognized that the requirement for the prospect of direct benefit might create ambiguity as to whether placebo-controlled clinical investigations may be conducted in children under this section. We stated that placebo-controlled clinical investigations in children may be conducted in accord with § 50.52. FDA invited comment on the issue of conducting placebo-controlled investigations in children. We also noted that there is evidence of direct benefit to children from participating in placebo-controlled trials, including increased monitoring and care of subjects,

even though a child may not actually receive the test product. This statement has been misinterpreted, and we provide clarification in the paragraphs that follow.

(Comment 6) Eight comments responded to FDA's request for comments on the issue of placebo-controlled clinical investigations in children. Five of the eight comments agreed with FDA that placebo-controlled trials in children may be appropriate in certain circumstances. Two comments opposed the conduct of placebo-controlled trials in healthy children, and one comment opposed the conduct of placebo-controlled trials in children with the active disease.

Of the five comments that supported the use of placebo-controlled clinical trials in children, four cited specific circumstances under which placebo-controlled trials would be appropriate in children. One comment stated that placebo-controlled trials should not be used in serious diseases where the absence of an "active substance" might put a child at undue risk. This comment stated that placebos should be used only in "benign" diseases such as the common cold or mild to moderate allergies because the absence of an active drug would not lead to a permanent handicap. The comment also stated a belief that in a controlled clinical trial, the active substance should be compared to the best standard therapy for the disease, so that children with a disease in a control group would be given the best standard therapy and not a placebo.

Another comment agreed with us that placebo-controlled trials may be conducted in accord with the terms of § 50.52. This comment stated that certain vaccines and a number of drug trials for certain non-life-threatening medical conditions may require use of placebo designs in which the placebo does not provide a medical benefit. This comment suggested that FDA evaluate specific circumstances on a study-by-study basis.

One comment noted that a prohibition or limitation on the use of placebo-controlled trials in children would not assist us in our goals of improving labeling and encouraging studies for

children. This comment also suggested that IRBs should retain broad latitude in determining whether or not a particular placebo-controlled trial holds out the prospect of direct benefit to the proposed subjects. This comment cited guidelines established by the research community (ICH E 10 (Ref. 6); American Academy of Pediatrics (Ref. 7)) as support for its position.

One comment agreed with FDA that placebo-controlled trials in children may be conducted if they are in accord with § 50.51 or § 50.52; however, this comment suggested that an IRB's determination of a prospect of direct benefit should be based primarily on the potential benefit of the research intervention itself. The comment suggested that FDA and HHS should develop guidance on what benefits should be taken into account when determining whether a protocol offers the prospect of direct benefit.

Two comments expressed specific support for the view, which they ascribed to the American Academy of Pediatrics, that placebos may be used ethically in children only if their use does not place children at increased risk. According to the comments, such increased risk includes not only risk of mortality or increased or irreversible morbidity, but also physical pain or other distress, including fear and inconvenience. These comments suggested codifying these points in the rule.

One comment was concerned with language in the preamble to the interim rule stating that clinical investigations under § 50.52 “generally are performed in children with the disease or condition for which the product is intended” (66 FR 20589 at 20593) (emphasis added). This comment suggested that when a product presents more than minimal risk to children, it should never be tested in children who do not have the disease or condition for which the product is intended. The comment stated a concern that healthy children are being recruited to participate in clinical trials and should not be exposed to risk unless their health is at stake. The comment

suggested that if children stand no chance of directly benefiting from the product being tested, their participation in such trials should be prohibited. Similarly, another comment stated that a healthy child should not be exposed to any degree of risk, even if the clinical investigation may benefit children with the disease.

One comment was opposed to the use of placebo-controlled trials in children. This comment stated that a child's development could be affected by the use of placebos in Phase 1 trials. The comment also stated that the use of placebos in Phase 2 trials could result in negative outcomes. This comment stated that the rule should clearly indicate that an investigational medicine would be compared against another "active medicine" in the same class.

We appreciate the numerous comments we received on this difficult area. Our position on the conduct of placebo-controlled trials in children takes into account the general guidance on the choice of control groups found in FDA's guidance entitled "International Conference on Harmonisation E 10 Choice of Control Group and Related Issues in Clinical Trials" (May 2001) (Ref. 6) and the advice of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Pediatric Subcommittee) and the Pediatric Ethics Subcommittee (PES) of FDA's Pediatric Advisory Committee (PAC). The PES and the PAC, and previously the Pediatric Subcommittee, are charged with providing advice and guidance on pediatric ethical issues.

In general, the Pediatric Subcommittee has agreed that placebo-controlled trials are acceptable in situations where there are no approved or adequately studied therapies for children with the condition under study. A Consensus Statement on the Pediatric Subcommittee's September 11, 2000, meeting is available on FDA's Web site at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077894.htm> (Ref. 8).

The PES met in June 2008 to address the interpretation of prospect of direct benefit as it relates to investigations conducted under the FDA subpart D regulations, including placebo-controlled trials (Ref. 9). The PES specifically addressed the question of what benefits may be considered “direct” under the FDA subpart D regulations, and whether the benefits need to accrue to children in both the control and treatment arms of a clinical trial. The general consensus of the PES was that the placebo arm of a trial cannot be considered to confer the prospect of direct benefit under § 50.52 of the FDA subpart D regulations. In general, the PES advised that the so-called “inclusion” benefit is not a “direct” benefit, and that children enrolled in the placebo arm of a trial should be exposed to no more than minimal risk or a minor increase over minimal risk (Ref. 9).

FDA agrees with this position. Because we do not consider the administration of a placebo to offer a prospect of direct benefit, part 50, subpart D, therefore requires that the placebo arm must present no more than minimal risk (§ 50.51) or a minor increase over minimal risk (§ 50.53), unless the clinical investigation is referred for review under § 50.54. As stated in ICH E10, in certain circumstances a placebo-controlled study of an investigational drug or biologic may involve the withholding of known effective treatment (section 2.1.3., Ref. 6). In such situations, however, the risks of such withholding of known effective treatment in the placebo control group should present no more than minimal risk or a minor increase over minimal risk, i.e. the placebo control arm of such a clinical trial must be approvable under either § 50.51 or § 50.53. The arm that receives the investigational product often would be approvable under § 50.52. With respect to the criteria that must be met for approval under § 50.53, we note that the inclusion of children without the disorder or condition under study would not meet the

requirement of § 50.53(c) that “the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition.”

With respect to the concern raised about physical pain or other distress, including fear and inconvenience, we recognize that children with a disorder or condition who are assigned to a placebo group might experience physical pain or discomfort (although no serious risk). It would usually be possible to design a trial to take this concern into account (for example by introducing "escape" or withdrawal provisions, such as defining an early escape as a treatment failure). Regardless of the trial design, however, for such a clinical trial to proceed, the risk of experiencing transient pain and/or discomfort would need to represent no more than a minor increase over minimal risk.

This approach to the analysis of placebo-controlled trials is consistent with the recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (created under the 1974 National Research Act, Public Law 93-348) that the interventions that do and do not offer a prospect of direct benefit in any given protocol must be analyzed separately (often called a component analysis of risk) (43 FR 2084 at 2086 (January 13, 1978)). This approach is applied to, for example, antimicrobial studies for the treatment of acute bacterial otitis media in the FDA guidance entitled “Acute Bacterial Otitis Media: Developing Drugs for Treatment” (September 2012) (Ref. 2).

(Comment 7) In the preamble to the interim rule, FDA discussed strategies for mitigating risk in clinical investigations, including exit strategies in the case of adverse events or a lack of efficacy or establishing a data monitoring committee (DMC) to review ongoing data collection and recommend study changes (66 FR 20589 at 20593). One comment suggested that while these strategies may be appropriate measures for an IRB when the clinical trial is conducted by

the IRB's institution, they may not be appropriate actions for a local IRB involved in a sponsored global clinical trial in which a DMC is part of the protocol and amendments are generated by the responsible sponsor.

Since we published the interim rule, we have issued a final guidance for clinical trial sponsors on the establishment and operation of clinical trial DMCs entitled "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees" (March 2006) (Ref. 10). This document discusses the role of DMCs and other oversight groups, including IRBs, and the relationship between sponsors and DMCs. As part of its initial evaluation, an IRB may appropriately inquire as to whether a DMC has been established and, if so, seek information about its scope and composition. For ongoing trials, an IRB is responsible for considering information arising from the trial that may bear on the continued acceptability of the trial at the study site(s) it oversees. A DMC generally has access to much more data than the IRB during the trial, including interim efficacy and safety outcomes by treatment arm, and makes recommendations with regard to the entire trial. Given its obligation to minimize the risks to patients, an IRB may take action based on information from any appropriate source, including recommendations from a DMC to the sponsor. A trial may have multiple IRBs, each responsible for the patients at a single site, but only one DMC. Individual investigators (or the sponsor of investigational devices) are responsible for assuring that IRBs are made aware of significant new information that arises about a clinical trial. Such information may include DMC recommendations to the sponsor that are communicated to IRB(s), either directly or through individual investigators or sponsors. Additionally, it may be useful for sponsors to ensure that IRBs are informed when DMCs have met, even when no

problems have been identified and the DMC has recommended continuation of the trial as designed.

3. Section 50.53--Clinical Investigations Involving Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, But Likely to Yield Generalizable Knowledge About the Subjects' Disorder or Condition

We solicited comments on § 50.53, particularly on whether further definitional criteria should be provided to aid IRBs in understanding certain concepts, including: (1) How to measure a minor increase in risk, (2) at what point a minimal risk develops into a major risk, and (3) whether IRBs have the expertise necessary to determine minor increases over minimal risk. We received four comments on this section.

(Comment 8) One comment expressed support for this provision, stating that the regulations provide adequate protections for children in research with more than minimal risk and provide IRBs with sufficient criteria for review. The comment stated that IRBs have been assessing “increases over minimal risk and the balance between the prospects of benefit to the individual participant or generalizable knowledge and can continue to make these assessments on a case-by-case basis.” Citing documents currently available to guide IRBs, the comment stated that there is no need for further definition or elaboration of criteria in the regulations. The comment concluded that additional criteria or definitions in the regulation would not provide greater protections for research participants.

In contrast, another comment expressed great concern regarding “the power that has been bestowed upon IRBs.” This comment stated that protection of pediatric populations requires a high degree of competency on the part of IRBs and pointed out that inappropriate practices have been detected in the past. The comment stated that only FDA should determine adequate

guidelines for the procedures and that we should be the only authority that decides whether a clinical investigation in this category goes forward.

Two comments on this section responded to our solicitation of comments on appropriate criteria for an IRB to use in assessing more than minimal risk. Both comments listed the critical factors as: (1) Age and degree of physiological maturity of the child, (2) nature and natural history of the clinical condition to be treated, (3) presence of complicating clinical conditions, (4) efficacy and safety of the treatment that may have been demonstrated in older patients, or that is expected on the basis of other clinical or preclinical investigations, and (5) likely duration of treatment and its impact upon the growth and development of the child.

We do not agree that only FDA should determine whether research in this category proceeds. Further, IRBs are required to comply with all applicable federal requirements, including those set forth in subpart D, in their review of clinical investigations. To the extent concerns have arisen, or may arise, concerning their compliance with Federal requirements, both OHRP and FDA have taken regulatory action against non-compliant IRBs and/or institutions and have worked to help eliminate non-compliant procedures used by IRBs.

Although there are many documents to guide IRBs in their decisionmaking, we recognize that further elaboration of the criteria set out in these final regulations may prove helpful. This may involve a long-term process of coordination with other Agencies, including OHRP. We appreciate comments received on the appropriate criteria for an IRB to use in assessing more than minimal risk and, although we are not incorporating these suggestions into the regulations at this time, we will consider these suggestions in the future. As previously stated, OHRP identified in its 2001 report to Congress the need for guidance on terms and concepts in HHS subpart D, including the terms “minimal risk,” “the prospect of direct benefit for the individual

subject,” “condition,” and “disorder” (Ref. 4) Should HHS propose changes to HHS subpart D, we will review and consider modifying the corresponding provisions of our regulations as appropriate.

4. Section 50.54--Clinical Investigations Not Otherwise Approvable That Present an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children

(Comment 9) We received five comments on this provision. One comment stated that the requirement for public review and comment on study proposals from private industry under § 50.54 “should be reconsidered in view of the commercial confidential nature of clinical drug development studies.” This comment suggested that a closed advisory committee meeting in which the committee would be supplemented with invited guests should permit full consideration of the issues and would satisfy the requirement for public review and comment. Three comments supported the requirement for public review and comment, with two of these comments recommending that FDA “suspend” a clinical trial referred under § 50.54 absent a sponsor’s willingness to publicly disclose the necessary information. One comment suggested that ethical issues would stem from the unwillingness of a sponsor to disclose needed information to the public, and that the “secrecy” of the clinical investigation and its conduct would raise suspicion and make people uncomfortable. The comment stressed that the rule should emphasize our authority to “suspend” clinical investigations pending the sponsor’s willingness to share information with the public after referral of the protocol for review under § 50.54.

Another comment requested that we clarify the requirements for the review of research under § 50.54. This comment stated that in cases where a research study involving children is

subject to both FDA and HHS regulations, it is unclear which entity will make the determination that the research can proceed, and that requiring a determination by both entities might be unnecessarily duplicative. The comment also noted that the preamble to the interim rule stated that FDA may not be able to provide public review and comment if the sponsor is unwilling to publicly disclose necessary information. The comment suggested that the text of the regulation state explicitly that public review and comment may not be possible in all cases given the FDA regulations relevant to sponsor confidentiality.

From the comments we received, it appears that confusion exists as to the intent of our statements in the preamble to the interim rule about the necessity of public review and comment. In the preamble we stated “Because FDA believes full public review and comment is critical in determining whether a clinical investigation should proceed under these circumstances, if a sponsor is unwilling to waive this privilege, FDA may not be able to satisfy the public review and comment requirement and any such clinical investigation could not proceed” (66 FR 20589 at 20594). The intent of this statement was to make it clear that if the public review and comment requirement could not be met because some or all of the information necessary for that public review and comment was trade secret and/or confidential commercial information, and therefore could not be discussed publicly unless the sponsor gave consent to have that information discussed publicly, the criteria under § 50.54 could not be met and thus the investigation could not go forward.

Because closed advisory committee meetings do not allow for public participation or review of issues under discussion, we do not agree that a closed advisory committee meeting satisfies the requirement for public review and comment. The Agency would be unable to

proceed with a referral of a clinical investigation involving children under § 50.54 unless there is full opportunity for public review and comment as provided in this section.

In December 2006, FDA published a final guidance document entitled "Guidance for Clinical Investigators, Institutional Review Boards and Sponsors; Process for Handling Referrals to FDA Under 21 CFR 50.54: Additional Safeguards for Children in Clinical Investigations" (Ref. 11). This final guidance describes the procedures FDA generally will follow in handling clinical investigations referred for review under § 50.54 and in reaching final determinations under this regulation. The guidance is based in part on FDA's experience to date with such referrals. This guidance also addresses situations in which a clinical investigation being referred involves an FDA-regulated product and is conducted or supported by HHS, and therefore is subject to both FDA's regulations (§ 50.54) and HHS regulations (45 CFR 46.407). If there is a referral of a clinical investigation subject to both FDA and HHS regulations, FDA's PAC is chartered to advise both the Commissioner of FDA and the Secretary of HHS on referrals under § 50.54 of FDA subpart D and § 46.407 of HHS subpart D.

OHRP's guidance on the review process under 45 CFR 46.407, issued in May 2005, is available on OHRP's Web page at http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html (Ref. 12).

D. Obtaining Assent From Children

We defined "assent" at § 50.3(n). In § 50.55 we listed our requirements for assent by children, and in the preamble to the interim rule we solicited comments on how to ensure that age-appropriate explanations are provided to children. We received three comments on soliciting and documenting assent and three comments on ensuring age-appropriate explanations.

(Comment 10) One comment suggested that the consent/assent of a child or family member should be witnessed by an independent person at the research facility and/or videotaped to ensure that proper and truthful information has been provided in an understandable fashion to children. A second comment requested that FDA define a minimum standard for documentation of assent similar to that of informed consent. The comment stated that a minimum standard would assist sponsors in monitoring and other quality assurance efforts and would facilitate increased consistency across clinical sites. The comment expressed concern that if an IRB determined that pediatric assent was warranted for a trial, but decided that documentation of the assent was unnecessary, both sponsors and FDA would be unable to determine that assent actually occurred. A third comment suggested that persons with demonstrated competence in dealing with children be added to the assent process to evaluate the cognitive levels of understanding for children in various age groups.

The requirements for assent listed at § 50.55 are the same as those in 45 CFR 46.408 of HHS subpart D. Because of the unique issues raised when soliciting assent from children, permission (i.e., consent) from one or both parents is required. This permission must be documented in accordance with and to the extent required by § 50.27. We do not agree that requiring an independent witness and/or videotape of the process of soliciting parental permission or child assent would, in every study, be necessary or would act as a safeguard. We conclude that the procedures in § 50.27 for documenting consent are sufficient for an adult providing parental or guardian permission. Additionally, in certain circumstances the use of videotape or the presence of an independent witness might intimidate a child being asked to provide assent. Under § 50.55(g), the IRB determines whether and how assent must be documented. If an IRB determines that videotaping the assent process is appropriate or that an

independent witness is warranted, the IRB can require such procedures at its discretion as a condition of study approval. We do not agree that adding a formal evaluation of the cognitive levels of understanding for children in various age groups is routinely warranted.

FDA's guidance entitled "E6 Good Clinical Practice: Consolidated Guidance" (ICH E6) (Ref. 13) recommends that a child "should be informed about the trial to the extent compatible with the [child]'s understanding and, if capable, the [child] should assent, sign and personally date the written informed consent" (§ 4.8.12, ICH E6, Ref. 13). In addition, the "language used in the oral and written information about the trial ... should be understandable" to the child or the child's parent or guardian (§ 4.8.6, ICH E6, Ref. 13). If a child is deemed capable of assent, and the assent requirement is not waived under § 50.55(c) or (d), the language used should be understandable to the child in order for the child's assent to be meaningful (§ 2.6.3, ICH E 11, Ref. 1). We are aware that some IRBs do not use a separate child assent form, preferring an oral explanation along with some form of documentation of a child's assent. At this time, we do not plan to articulate a single standard similar to informed consent for obtaining or documenting assent. Although adults are presumed to have the level of competency necessary to grant informed consent, children's levels of competency differ on an individual basis, and therefore there is no one standard that would or could apply to all situations. In § 50.55, we have stated our requirements for the assent process and left IRBs discretion to determine whether children in a particular study are capable of providing assent. IRBs must determine for the clinical trial as a whole, or for each child or group of children within a trial, the appropriateness of obtaining assent, the ability of children to understand the subject of their assent, and the method of documentation appropriate to that understanding. Similarly, while we encourage IRBs to require documentation of assent when appropriate, as evidenced by § 50.55(g), we consider the issue of

whether and how to document assent as appropriately left to the discretion of the IRB based on its own assessment. The requirement that in all cases parental or guardian permission must be granted and documented in accordance with and to the extent required by § 50.27 acts as a safeguard to the assent process.

(Comment 11) Three comments responded to our solicitation on ensuring age-appropriate explanations to children. The first comment stated that age-appropriate assent has long been a part of the HHS regulations and that current, available guidance is sufficient to assist IRBs in meeting their responsibilities. This comment stated that there is no need for further definition or elaboration of criteria to aid IRBs in ensuring age-appropriate explanations. A second comment stated that FDA should encourage the study and publication of techniques for securing the assent of pediatric patients. A third comment stated that ensuring that children are provided with age-appropriate explanations is both important and difficult. The comment supported the factors listed in the regulation and added the following factors: The environment in which the research will be conducted, the expertise of the researchers, and the risks and benefits of the specific protocol. The comment concluded that since these are matters of informed judgment, the assessment of the appropriateness of the explanation to children at a particular research site is best made by a duly constituted IRB that, as necessary, consults with individuals with expertise and experience in age-appropriate explanations.

We agree with the comment that ensuring that children are provided with age-appropriate explanations is important and difficult. We also agree that the assessment of appropriateness is best left to the IRB responsible for review of any specific protocol. However, if child assent is required, persons who are knowledgeable and skilled in dealing with children should be involved in the assent process to detect and/or minimize child distress (§ 2.6.3 and 2.6.5; ICH E 11, Ref.

1). While we acknowledge that age-appropriate assent has long been a part of HHS regulations, we support the continued study and publication of techniques for securing the assent of pediatric patients in the best ways possible.

E. Waiver of Permission

Consistent with the interim rule, we are not adopting the provisions of HHS subpart D at 45 CFR 46.408(c) that allow IRBs to waive the requirements for obtaining permission in certain circumstances. The policy decision not to adopt the waiver of parental or guardian permission found in 45 CFR 46.408(c) stems from FDA's specific regulatory scheme. We explained in the preamble to the interim rule that the only exceptions to our requirements for informed consent are found in the emergency exceptions listed in part 50 of our regulations.

(Comment 12) We received six comments on this provision. Four comments supported our decision not to adopt the waiver provision for permission by parents or guardians. Two comments objected to our decision not to adopt the waiver provision.

Of the two comments that objected to our decision not to adopt the waiver provision, one comment suggested that the waiver provision for parental permission in HHS subpart D is appropriate in certain, unusual circumstances and suggested that we adopt it in limited, appropriate circumstances. The comment provided two possible examples of circumstances it considered unusual: (1) The development of a new test kit for a sexually transmitted disease or (2) studies involving children who have been the victims of sexual abuse. The comment also asked that FDA clarify that the option to waive informed consent in emergency settings applies to pediatric research and that FDA specifically state that the possible exceptions in § 50.24 apply to children as well.

The other comment that objected to our decision not to adopt the provision for waiver of parental permission asked us to interpret the FD&C Act to enable mature adolescents to consent to involvement in certain types of clinical studies without parental permission. The comment stressed that if such an interpretation of the law is not possible, we should seek to change the law to allow FDA and HHS regulations to be consistent in this area. The comment stated that if the waiver provision is not adopted, vital research involving mature adolescents for whom seeking parental permission is not in their best interest will not be conducted.

The comment cited the example of research studies using new therapeutic modalities for the human immunodeficiency virus (HIV) and the acquired immunodeficiency virus (AIDS) in the HIV epidemic in the late 1980s and early 1990s and stated that many adolescents who sought treatment for HIV requested that their diagnosis be kept confidential from their parents. The comment stated that such confidential treatment was provided to these adolescents based on State laws allowing physicians to treat adolescents for sexually transmitted diseases without parental involvement. The comment continued that when new drugs became available only under research protocols, these adolescents would not have been afforded the potential benefits from participation in such clinical trials if parental permission were required. The comment stated that clinicians responded to this problem by asking IRBs to invoke 45 CFR 46.408(c) of HHS subpart D to allow the research to proceed without informing the parents of adolescents who requested confidentiality. This comment also urged the development of guidance to protect the interests of adolescents and children who are research subjects.

We have reviewed this issue and have decided not to adopt the waiver of parental or guardian permission. We acknowledge that FDA and HHS regulations are not harmonized on this point; however, as discussed in the paragraphs that follow, we consider this difference to be

necessary and appropriate in light of FDA's existing statutory and regulatory scheme.

Furthermore, we conclude that, notwithstanding the decision not to adopt the waiver of parental or guardian permission, FDA's regulations will ensure that, as required by section 2701 of the Children's Health Act, all FDA-regulated clinical investigations are in compliance with 45 CFR part 46. Section 46.408(c) of HHS subpart D does not represent a requirement that must be met in order for a clinical investigation to be conducted in compliance with HHS subpart D; rather, this waiver provision allows for a waiver of certain requirements of HHS subpart D.

We recognize that mature adolescents may contract diseases such as HIV-AIDS and other sexually transmissible diseases, and that there are important issues relating to the confidentiality of treatment sought. We note that in some situations a State may grant certain classes of mature adolescents of a specific age the right to consent to treatments or procedures involved in a clinical investigation. These mature minors would not meet the definition of children under § 50.3(o) and thus would not be subject to the requirements of this subpart. Similarly, minors deemed "emancipated" by state law also would not meet the definition of children under § 50.3(o) and would not be subject to the requirements of this subpart. Mature or emancipated minors would be allowed to consent to participation in FDA-regulated research without the need for parental or guardian permission. Thus, we consider reliance on established state and/or local laws that establish an adolescent as mature and/or emancipated to be appropriate in this context. Furthermore, it would be difficult to limit the interpretation and application of a waiver provision to narrowly apply to a limited set of circumstances or appropriate conditions, as suggested by one comment.

In FDA's view, adopting the waiver provision in 45 CFR 46.408(c) would be prohibited by the FD&C Act in certain circumstances, and would be inconsistent with FDA's implementing

regulations. Specifically, section 520(g)(3) of the FD&C Act, which was added to the FD&C Act as part of the Medical Device Amendments of 1976 (Public Law 94-295), requires that informed consent be obtained from each human subject in a clinical trial of a device, except when an exception is granted in certain narrow emergency situations. Thus, the circumstances in which an exception from the requirement for informed consent can be granted in a clinical investigation of a medical device are specifically set forth in FDA's statute. When FDA issued its informed consent regulations (46 FR 8942, January 27, 1981), the agency sought to create a single set of informed consent regulations (part 50), including provisions for an exception from the requirement for informed consent, that would provide consistent protections for subjects in trials subject to FDA jurisdiction, regardless of the type of product being investigated. Accordingly, the provisions in part 50 pertaining to exceptions from the requirement for informed consent are based on those in section 520(g)(3) of the FD&C Act, and apply to all FDA-regulated clinical investigations.

Because parental or guardian permission takes the place of informed consent when the human subject is a child, a waiver of permission (as in 45 CFR 46.408(c) of the HHS regulations) is equivalent to a waiver of or exception from the requirement for informed consent, regardless of whether child assent is obtained. If we were to amend our regulations to allow for IRB waiver of or exception from the requirement to obtain permission in certain clinical investigations involving children, we would be prohibited from doing so by section 520(g)(3) of the FD&C Act with regard to medical device trials. Thus, we would have two disparate standards of human subject protection (one for clinical trials of devices and one for other trials regulated by FDA) based not on ethical considerations, but rather based solely on the type of product being studied. We conclude that this result would not be in the interest of public health

and safety, and that public health and safety is best served by having uniform informed consent requirements across medical product categories and that the informed consent requirements should not vary depending on whether a clinical trial regulated by FDA involves a drug, biological product, device, or other product subject to FDA jurisdiction.

We note that § 50.23 sets forth an exception from the general requirement to obtain informed consent in certain situations when a human subject is confronted by a life-threatening situation necessitating the use of a test article when there is not sufficient time to obtain consent from the subject or the subject's legal representative. FDA interprets this provision to apply to children when there is not sufficient time to obtain parental or guardian permission. The regulation therefore allows a test article to be administered to a child if the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing, before use of the test article, that certain conditions are met, including that there is no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the child. However, § 50.23 also provides that, if immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject (in this context, the child), and time is not sufficient to obtain the required independent determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. In either situation, the written documentation must be submitted to the IRB within 5 working days after the use of the test article.

With regard to the concerns in the comment about emergency research involving children, we wish to clarify that the emergency research provisions in § 50.24 apply, and always

were intended to apply, to clinical investigations involving children. We have added language to § 50.55(e) that originates from § 46.408(b) of HHS subpart D and was inadvertently omitted from the interim rule, indicating that the exceptions from informed consent for emergency research described in § 50.24 apply to research in children. Section 50.55(e) now reads, “In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine, in accordance with and to the extent that consent is required under part 50, that the permission of each child’s parents or guardian is granted” (emphasis added). This change is being made to confirm that the emergency provisions in part 50 apply to clinical investigations involving children.

F. Wards

(Comment 13) We received five comments on the participation of children who are wards in clinical investigations. One comment supported the appointment of an advocate for children who are wards. One comment asked for clarification about the appointment process, noting that the preamble to the interim rule states that the IRB itself must appoint the advocate rather than assure that an advocate has been appointed. Two comments asked for clarification about the role and responsibilities of an advocate, and the obligations of a central IRB and sponsor in monitoring the appointment of advocates. One comment stated that the text of the preamble overstated the meaning of § 50.56 by specifying that an IRB appoint an advocate for each child, noting that an IRB-appointed advocate would essentially duplicate the role of an advocate who may already have been appointed by the State or any other agency, institution, or entity. The comment stated that the role of the IRB should be to review and confirm that an advocate who meets the requirements of § 50.56 has been appointed. The comment stated that the advocate need not be the same individual appointed by the State to serve as a guardian or in

loco parentis and that IRBs should be empowered to reject the selection of the advocate presented for confirmation if the IRB believes that individual to be unsuitable.

We agree with the comment that the preamble overstated the requirement, as set forth in § 50.56, for the appointment of an advocate. As § 50.56 states, the IRB must require appointment of an advocate for each child who is a ward, not appoint the advocate itself. This advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis and will act in the best interest of the child for the duration of the child's participation in the clinical investigation. We note that § 50.56 only addresses the circumstances in which wards can be included in clinical investigations approved under § 50.53 or § 50.54, and therefore only requires the appointment of an advocate in such clinical investigations. It does not address the appointment of an advocate in clinical investigations approved under § 50.51 or § 50.52; however, the regulations do not preclude an IRB from considering the appointment of an advocate in such clinical investigations in order to assure that there is someone who will act in the best interest of the child for the duration of the child's participation in the clinical investigation. Before enrolling any child who is a ward in a clinical investigation, IRBs should ensure that each child has a guardian and/or advocate with the background, experience and commitment to act in the best interest of the child.

We do not consider it necessary to codify a provision specifically empowering the IRB to reject the selection of an advocate if the IRB finds that individual to be unsuitable. Other regulatory provisions, including § 56.113, provide the IRB with authority to suspend or terminate research if it determines that any aspect of the research is not in conformance with the regulations. This would include any noncompliance with § 50.56.

G. Biological Products

(Comment 14) One comment requested that we clarify that the regulations apply to biological products. Section 50.1 of part 50--Protection of Human Subjects, and § 56.101 of part 56--Institutional Review Boards, clearly state that they apply to clinical investigations regulated by FDA under sections 505(i) and 520(g) of the FD&C Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA, including human drug and biological products; medical devices for human use; foods, including dietary supplements, that bear a nutrient content claim or health claim; infant formula; food and color additives; and electronic products. Because §§ 50.1 and 56.101 apply to this final rule, it is unnecessary for us to include specific language in this final rule indicating that it applies to biological products.

H. Economic Analysis

We received three comments on the economic analysis in the interim rule.

(Comment 15) One comment stated that the estimate of additional time to be spent by IRBs to review and document the level of risk may be underestimated at one person-hour. The comment also raised concern that the additional IRB responsibilities, including ensuring age-appropriate explanations for assent and assessing strategies for the appointment of advocates, will add to the time spent by IRBs to ensure the safe conduct of pediatric clinical trials. The comment requested clarification on the nature and scope of the documentation necessary.

Under current regulations and guidance, IRBs are already required to make several determinations concerning risk to participants and to document those risks. The additional requirements of this rule state that IRBs must specifically identify which of the four risk categories applies to children in a clinical trial. We expect that this determination will require

some additional effort, but take at most one person-hour of additional time. This estimate includes time for the documentation required to identify the selected risk category.

(Comment 16) Two comments stated that they did not agree with our assumption that there would be no costs associated with clinical holds. These comments noted that we did not calculate the potential impact of the widespread accreditation of IRBs. These comments stated that inspection of studies will be common as IRBs go through the accreditation process and that, particularly in the pediatric area, IRBs themselves may increase their inspection of studies to avoid findings of “noncompliance” by accrediting bodies. The comments concluded that increased inspections will probably uncover more circumstances in which studies will be put on clinical hold.

This rule does not require IRBs to undergo any accreditation process. We do not know of any plans to require federally mandated accreditation of IRBs, nor do we endorse any particular accreditation body. Therefore, there are no costs from accreditation related to this rule. While IRB reviews of pediatric clinical trials may become more comprehensive if there are concerns about noncompliance, any increase in IRB reviews because of noncompliance would not be attributable to this rule, but to problems with noncompliance generally.

I. Requests for Additional Requirements

(Comment 17) Two comments raised concerns that ethical standards were not codified in the regulation. One comment called on us to ensure that the pharmaceutical industry focuses on the ethical conduct of clinical trials in children and not financial gain. The other comment raised concern that the regulations do not include standards for conflict of interest or require that such conflicts by investigators or institutions be revealed on informed consent documents to parents or guardians. The comment also noted that the regulations do not mention rules for recruitment.

This comment suggested that there should be prohibitions against “bribing” parents with high payments to offer their children for research and that compensation should cover only direct expenses such as travel, meals and lodging costs, and daycare for other children.

FDA’s regulations under 21 CFR part 54 govern financial disclosure by clinical investigators and requires disclosure of certain financial relationships between the sponsors of covered studies and the clinical investigators, including interests of the clinical investigators in the product under study or in the sponsor of the covered studies. We use this information in conjunction with information about the design and purpose of the study, as well as information obtained through onsite inspections, in our assessment of the reliability of data presented.

In August 2000, HHS held a conference on human subject protection and financial conflicts of interest. As a result of this conference, HHS issued a final guidance in May 2004 entitled “Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection” (Ref. 14). Since that time, FDA has issued additional guidance related to this issue, including a draft guidance issued in May 2011 entitled “Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators” (Ref. 15), and a final guidance issued in October 2009 entitled “Guidance for Industry: Investigator Responsibilities--Protecting the Rights, Safety, and Welfare of Study Subjects” (Ref. 16).

Additionally, we note that ethical considerations for IRBs are covered under several provisions of our regulations. Sections 56.107(a) and 56.111 require IRBs to ensure that appropriate safeguards exist to protect the rights and welfare of research subjects. In fulfilling these responsibilities, an IRB is expected to review all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. The protocol, the

consent document and, for studies conducted under the Investigational New Drug (IND) regulations, the investigator's brochure are examples of documents that the IRB should review. The IRB should also review the methods and material that investigators propose to use to recruit subjects (see “Recruiting Study Subjects--Information Sheet,” Ref. 17). Section 56.107 on IRB membership contains several provisions designed to prevent conflicts of interest. Section 56.107(e) states that no IRB may have a member participate in the IRB’s initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

Regulatory requirements for recordkeeping and retention of records provide one means for FDA oversight of IRBs. Section 56.115(c) states that we may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow inspections of its records or reports. Similarly, subpart E of part 56 outlines various actions we may take against IRBs if we observe during an inspection that an IRB is not complying with the regulations. These actions include disqualification of an IRB, referral for civil or criminal judicial proceedings, and any other appropriate regulatory action. We may also refer matters to another Federal, State, or local government Agency for any action that the Agency determines to be appropriate.

Although it is always possible that an IRB will not be in compliance with all of our regulations, our current IRB regulations, along with other human subject protection regulations, provide us with multiple tools to ensure ethical conduct by IRBs, clinical investigators, and sponsors. The 2001 OHRP report identified the need for guidance on payment (financial or otherwise) that may be provided either to children involved in research as subjects or to their parents, under circumstances that minimize the possibility of coercion or undue influence (Ref.

4). While the 2004 IOM report concluded that payments related to research participation have a role to play in reducing barriers and equalizing access to research participation, it recommended that IRBs should develop written guidance and policies on payments to children or parents related to research participation (Ref. 5). Should HHS propose changes to its regulations pertaining to IRB oversight, we will review our regulations and consider revising them as appropriate.

IV. Legal Authority

This rule finalizes the interim rule published in 2001 to bring FDA regulations into compliance with provisions of the Children's Health Act (Public Law 103-310). Title XXVII, section 2701 of the Children's Health Act required that within 6 months of enactment all research involving children that is conducted, supported, or regulated by HHS be in compliance with HHS regulations providing additional protections for children involved as subjects in research. The HHS regulations are codified at 45 CFR part 46 subpart D. FDA interprets the Children's Health Act to require FDA to issue regulations to ensure that clinical investigations of FDA-regulated products are conducted in compliance with HHS subpart D.

Additional authority for this rule derives from sections 505(i) and 520(g) of the FD&C Act regarding clinical investigations of FDA-regulated drugs, biological products, and devices for human use. These provisions direct the Commissioner to issue regulations for exempting such investigational products from the general requirements for preapproval or presubmission review. Among other stated objectives, this final rule fulfills that mandate by enhancing protections for children involved as subjects in clinical research of FDA-regulated drugs, biological products, and devices for human use.

A further source of authority for this rule is section 701 of the FD&C Act (21 U.S.C. 371), which authorizes the Commissioner to issue regulations for the efficient enforcement of the FD&C Act. This final rule helps the efficient enforcement of the FD&C Act by enhancing clarity and certainty in FDA's oversight of clinical investigations involving children as subjects.

V. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act

This final rule contains no new collection of information under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501- 3520), and therefore review by the Office of Management and Budget (OMB) is not required. The information requested for clinical investigations in children of FDA-regulated products is already covered by the collections of information in the IND regulations (21 CFR part 312), the investigational device exemption (IDE) regulations (21 CFR part 812), the IRB regulations (§ 56.115), the food additive petition and nutrient content claim petition regulations (21 CFR 101.69 and 101.70), and the infant formula regulations (21 CFR parts 106 and 107), all of which are approved by OMB. Specifically, the information collected under the IND regulations is currently approved under OMB control number 0910-0014. The information collected under the IDE regulations is currently approved under OMB control number 0910-0078. The information collected under the IRB regulations is currently approved under OMB control number 0910-0130. The information collected in food additive and nutrient content claim petitions is currently approved under OMB

control number 0910-0381 (general requirements) and 0910-0016 (FDA Form 3503). The information collected under the infant formula regulations is currently approved under OMB control number 0910-0256 (general requirements) and 0910-0188 (infant formula recalls).

VII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this final rule is not a significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The Agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$139 million, using the most current (2011) Implicit Price

Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Updated Analysis

The interim final rule (66 FR 20589 at 20596, April 24, 2001) imposed an additional burden on IRBs reviewing investigations which involve children. The estimated costs of the interim final rule were estimated to be small (\$933,000 in year 2001 and \$23,550 per year in years 2002 through 2009). As the interim final rule has been in effect since April 2001, the publication of this final rule will have little additional impact. However, we update the estimated costs of the interim rule for the post-2001 period to adjust for inflation and availability of more recent data. The total annual cost of reviewing pediatric clinical trials remains at \$933,000 (this includes a one-time cost of \$900,000 to conduct a one-time review and update standard operating procedures plus \$33,000 for annual reviews) for the year 2001. The revised annual review cost for the post-2001 period ranges between \$79,817 and \$112,357 per year (see table 1 in this document).

The revised post-2001 costs per year are revised as follows. First, the annual IRB costs per year are in inflation-adjusted (2010) dollars. Second, we use recent data from the various FDA centers reviewing protocols involving pediatrics, and update the total number of studies affected by the rule to be between 872 and 1,227 per year. We note that given data limitations we are unable to use the same period of analysis across centers. To the extent that there has been an increase in the number of protocols involving children since 2001, then using the most recently available data would provide an upper bound estimate on the average number of protocols received after 2001. However, over the past few years, most offices within FDA's Center for Drug Evaluation and Research (CDER) did not observe a significant increase in the percentage

change of protocols received. Thus, we believe that the impact of using different periods of data is negligible. The data and methodology used are discussed in more detail in the paragraphs that follow.

The estimated number of drug- and biologics-related protocols involving pediatrics ranges from 561 to 637. The number of drug-related or biologics-related protocols (553 to 610) provided by CDER was based on data from fiscal year 2011. The range of protocols related to biological products regulated by FDA's Center for Biologics Evaluation and Research (CBER) represents the minimum (8 in fiscal year 2004) and maximum (27 in fiscal year 2011) number of pediatric protocols received by CBER during fiscal years 2002-2011. The count is adjusted up 30 percent¹ to account for IND-exempt protocols.

We estimate that 305 to 572 medical device protocols involve pediatrics. This is calculated by using the average number of applications or submissions (including supplements) reviewed by FDA's Center for Devices and Radiological Health per year and an estimate on the percent of medical device applications involving children. We estimate that, using the number of approved IDE pediatric studies as reported by FDA's Center Tracking System (7 to 13), and the average number of original IDE submissions (219) in fiscal years 2008-2009, 3 percent to 6 percent of medical device protocols involve pediatrics. We note that there could be some high-risk medical devices which might not be included in our estimated number of protocols for medical devices; however, data limitations do not permit us to quantify the extent to which our estimates would have to be adjusted up.

Finally, the estimated number of protocols for food additives and infant formula are extrapolated using the average High-to-Low ratio (3-to-1) across the other products and the

¹ This estimate is determined based on discussions with academic and commercial IRBs on the estimated percent of pediatric protocols which are exempt from filing an IND application.

initial estimates in the final rule. For instance, to determine the upper-bound estimate for infant formula we multiply the 2001 estimate by the High-to-Low ratio (5 x 3).

Table 1.--Estimated Number of IRB Reviews per year for Clinical Investigations in Children			
		Per year post-2001	
	2001	Low	High
Drugs and Biological Products	264	561	637
Medical Devices	170	305	572
Foods and Food Additives			
Infant Formula	5	5	15
Food Additives	1	1	3
Total IRB Reviews per year	440	872	1,227
Total IRB Costs per year	\$33,000	\$79,817	\$112,357

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. References

The following references have been placed on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857 and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through

Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified the Web site addresses, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. FDA “Guidance for Industry: ICH E11 Clinical Investigation of Medicinal Products in the Pediatric Population,” December 2000, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073143.pdf>, accessed June 21, 2012.

2. FDA “Guidance for Industry: Acute Bacterial Otitis Media: Developing Drugs for Treatment,” September 2012, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070947.pdf>, accessed October 15, 2012.

3. FDA “Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children,” March 2007, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071968.pdf>, accessed June 21, 2012.

4. OHRP “Protections for Children in Research: A Report to Congress in Accord with Section 1003 of P.L. 106-310, Children’s Health Act of 2000,” May 2001, available at:

<http://www.hhs.gov/ohrp/archive/reports/ohrp502.pdf>, accessed June 21, 2012.

5. Committee on Clinical Research Involving Children, Board on Health Sciences Policy, Institute of Medicine of the National Academies, “Ethical Conduct of Clinical Research Involving Children,” Marilyn J. Field and Richard E. Behrman, Eds., The National Academies Press, 2004, available at

<http://www.iom.edu/Reports/2004/Ethical-Conduct-of-Clinical-Research-Involving-Children.aspx>, accessed June 21, 2012.

6. FDA “Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials,” May 2001, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073139.pdf>, accessed June 25, 2012.
7. Committee on Drugs, American Academy of Pediatrics, “Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations,” *Pediatrics*, vol. 95, No. 2, pp. 286-294, February 1995.
8. FDA “FDA Pediatric Ethics Working Group Consensus Statement on Pediatric Advisory Subcommittee’s September 11, 2000,” available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077894.htm>, accessed June 25, 2012.
9. FDA Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, June 9-10, 2008 meeting. The agenda, briefing information, slides, minutes and transcripts can be found at <http://www.fda.gov/ohrms/dockets/ac/oc08.html#pac>, accessed June 27, 2012. Relevant excerpts of the transcripts are on display in the FDA Division of Dockets Management.
10. FDA “Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees,” March 2006, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>, accessed June 25, 2012.
11. FDA "Guidance for Clinical Investigators, Institutional Review Boards and Sponsors; Process for Handling Referrals to FDA Under 21 CFR 50.4: Additional Safeguards for Children in Clinical Investigations, " December 2006, available at

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127605.pdf>, accessed June 25, 2012.

12. HHS Office of Human Research Protections “Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process,” May 2005, available at http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html, accessed on June 25, 2012.

13. FDA “Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance,” April 1996, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf>, accessed June 25, 2012.

14. Department of Health and Human Services, “Final Guidance Document: Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection” May 2004, available at <http://www.hhs.gov/ohrp/policy/fguid.pdf>, accessed June 25, 2012.

15. FDA "Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators,” May 2011, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM256525.pdf>, accessed June 25, 2012.

16. FDA “Guidance for Industry: Investigator Responsibilities--Protecting the Rights, Safety, and Welfare of Study Subjects,” October 2009, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>, accessed on June 25, 2012.

17. FDA “Recruiting Study Subjects--Information Sheet. Guidance for Institutional Review Boards and Clinical Investigators,” page last updated: 10/18/2010, available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>, accessed June 25, 2012.

List of Subjects

21 CFR Part 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

21 CFR Part 56

Human research subjects, Report and recordkeeping requirements, Safety.

Accordingly, the interim rule amending 21 CFR parts 50 and 56 which was published at 66 FR 20589, on April 24, 2001, is adopted as a final rule with the following changes:

PART 50--PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 21 CFR part 50 continues to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.

§ 50.3 [Amended]

2. Amend § 50.3 by revising paragraphs (n), (r), and (s) to read as follows:

§ 50.3 Definitions.

* * * * *

(n) Assent means a child’s affirmative agreement to participate in a clinical investigation. Mere failure to object should not, absent affirmative agreement, be construed as assent.

* * * * *

(r) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation.

(s) Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

3. Revise § 50.51 to read as follows:

§ 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds that:

(a) No greater than minimal risk to children is presented; and

(b) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in § 50.55.

4. Revise the introductory text of § 50.52 to read as follows:

§ 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds that:

* * * * *

5. Revise the introductory text of § 50.53 to read as follows:

§ 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds that:

* * * * *

6. Revise paragraph (a) of § 50.54 to read as follows:

§ 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

* * * * *

(a) The IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

* * * * *

7. Revise paragraph (e) of § 50.55 to read as follows:

§ 50.55 Requirements for permission by parents or guardians and for assent by children.

* * * * *

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine, in accordance with and to the extent that consent is required under part 50, that the permission of each child's parents or guardian is granted.

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for clinical investigations to be conducted under § 50.51 or § 50.52.

(2) Where clinical investigations are covered by § 50.53 or § 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

* * * * *

PART 56--INSTITUTIONAL REVIEW BOARDS

8. The authority citation for 21 CFR part 56 continues to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.

9. Revise in § 56.109 the second sentence of paragraph (h) to read as follows:

§ 56.109 IRB review of research.

* * * * *

(h) * * * When some or all of the subjects in a study that was ongoing on April 30, 2001, are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D of this chapter, either at the time of continuing review or, at the discretion of the IRB, at an earlier date.

Dated: February 21, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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